PCT/AU00/00638

AU00/00638

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WITNESS my hand this
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AUSTRALIA

Patents Act 1990

CRC for Biopharmaceutical Research Pty Ltd

PROVISIONAL SPECIFICATION

Invention Title:

Method of treatment

The invention is described in the following statement:

Method of treatment

FIELD OF THE INVENTION

The present invention relates to method of treating carcinoma using antibody therapy. In particular the present invention relates to a method of ameliorating or preventing adverse side effects associated with such therapy.

BACKGROUND OF THE INVENTION

Regulatory agencies have recently approved the use of a number of antibodies for the treatment of cancer. Herceptin, was approved by the US food and Drug Administration (FDA) in September 1998 for the treatment of metastatic breast cancers which overexpress HER-2/neu. The drug is used as first line therapy in combination with paclitaxel, and as a single agent in second and third line therapy.

The FDA approved Rituxan for the treatment of patients with relapsed or refractory low-grade or follicular, CD20 positive B-cell non-Hodgkin's lymphoma in November 1997. Rituxan was the first monoclonal antibody licensed for treatment of cancer in the United States.

In 1994 the monoclonal antibody 17.1A (Panorex) was approved for the adjuvant treatment of colorectal cancer in Germany. Panorex was the first monoclonal antibody approved for use in the treatment of malignancy.

C30.6 is a chimeric monoclonal antibody that recognises an antigen expressed on more than 90% of colorectal carcinomas (1). This antibody has been shown to mediate antibody dependent cellular cytotoxicity (ADCC) *in vitro* (2). Anti-tumour effects have also been demonstrated *in vivo* in animal models (2).

The present inventors have recently initiated a Phase I clinical trial of c30.6 in patients with advanced colorectal cancer.

In Australia, 3,000 deaths occur annually as a result of colorectal cancer, making it the second most common cause of death from malignancy. In New South Wales the incidence of colorectal cancer is 61.1 per 100,000 males and 48.9 per 100,000 females (NSW Central Cancer Registry, 1994). At diagnosis, colorectal cancer may be local (stage I or II; Dukes A or B), regional (stage III; Dukes' C) or advanced/metastatic (stage IV; Dukes' D). At the time of diagnosis 30% of patients will have advanced incurable disease. For the remaining patients surgery represents

the mainstay of treatment, however approximately 40% of these patients will develop a recurrence within 5 years of surgery. The best predictor of relapse following surgery is the disease stage and extent of nodal involvement with tumour. Node negative patients have a 5 year survival of 65-97% while the survival in the node positive group ranges from 30-74%. A number of large studies have clearly demonstrated that adjuvant chemotherapy improves the disease free and overall survival of individuals with Stage III disease. Standard current regimens include 5-fluorouracil (5-FU) and leucovorin. These drugs have also shown activity in the treatment of metastatic disease although the response rates are usually less than 20%.

The murine monoclonal antibody 17-1A was the first monoclonal antibody approved for use in the treatment of malignancy and is currently under investigation for the adjuvant treatment for patients with stage III colon cancer. During the 1980s, 17-1A was used in clinical trials to treat over 300 patients with metastatic gastrointestinal cancer without any evidence of response or improved survival (3). In 1985 a randomised placebo controlled trial using 17-1A as adjuvant therapy for Dukes' stage C colorectal cancer was initiated in Germany (4). A total of 189 patients were enrolled, with 90 patients in the observation arm and 99 in the treatment arm. After a median follow up of five years, treatment with 17-1A was associated with a statistically significant reduction in death rate (51% vs 36% in the observation arm, $p=0.043$) and disease free recurrence (66% vs 48% in the observation arm $p=0.027$). The seven year follow-up data on this study corroborate the five year results, with antibody treatment reducing mortality by 32% ($p<0.01$) and disease recurrence by 23% ($p=0.04$) (5). These results are comparable with that obtained with standard adjuvant chemotherapy, using either one year of 5FU and levamisole, or six months of 5FU and leucovorin (6, 7).

The ability of antibodies to kill resting cells provides a good rationale for the use of these agents in combination with chemotherapy. This issue is currently being addressed by two international phase III trials in Dukes' stage C colon cancer (8). The first, in the United States and Canada, is comparing 17-1A plus 5FU/levamisole with 5FU/ levamisole in 1800 patients. The second study, which involves 2,700 patients from over 170 centres in 23 countries, has three treatment arms comparing 17-1A alone, 17-1A plus 5FU/Folinic acid and 5FU/Folinic acid (8). This study has now completed

enrolment. Other studies currently in progress include an Austrian study of 1000 patients evaluating 17-1A, chemotherapy and radiotherapy in Dukes' stage B and C rectal cancer, and a phase III study of 1500 Dukes' stage B2 colon cancer patients in North America. These clinical studies using 17-1A have also demonstrated that it has less severe and qualitatively different side effects when compared with 5 FU. This feature together with its shorter administration time may make it a useful agent on its own in patients who are unable to tolerate chemotherapy.

These clinical studies provide evidence that immunotherapy will be useful in the treatment of colorectal cancer, especially in the setting of minimal residual disease. However, the response of patients with end-stage metastatic disease is not a good predictor of response in the adjuvant setting and multi-centre are required for the evaluation of adjuvant therapy. For these reasons, localisation of radiolabelled antibodies has been proposed as a surrogate marker of potential antibody targeting and hence efficacy.

c30.6 antibody

The present inventors' studies indicate that chimeric 30.6 antibody has several significant advantages over other antibody products (such as Panorex), specifically,

- Narrower tissue cross-reactivity
- Higher affinity for its target antigen
- Engineered to provide optimal effector activity and minimal mouse components.

SUMMARY OF THE PRESENT INVENTION

The present inventors have found, however, that the administration of the 30.6 antibody leads to adverse side effects. The present inventors have found that these side effects may be ameliorated or prevented by pre-administration of H1 and/or H2 receptor antagonists.

Accordingly, in a first aspect the present invention consists in a method of treating colorectal carcinoma in a subject, the method comprising administering to the subject 30.6 antibody wherein prior to administration of the antibody H1 and/or H2 receptor antagonists are administered to the subject.

In a second aspect the present invention consists in a method of ameliorating or preventing at least one adverse side effect associated with the administration of 30.6 antibody to a subject, the method comprising administering H1 and/or H2 receptor antagonists to the subject prior to administration of the 30.6 antibody.

In a preferred embodiment of the present invention phenergan and/or Zantac, preferably both, are administered to the subjects prior to administration of 30.6 antibody. Preferably the antagonists are administered at least one hour prior to 30.6 antibody administration. Preferably the H-1 antagonist is administered in large doses.

Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

The disclosure of all references referred to in this specification are included herein by cross-reference.

DETAILED DESCRIPTION OF THE INVENTION

In order that the nature of the present invention may be more clearly understood preferred forms thereof will now be described with reference to the following non-limiting examples.

The clinical study

The primary objective was to evaluate the safety and immune responses to intravenously administered chimeric 30.6 antibody (c30.6) in patients with metastatic colorectal cancer.

The secondary objectives were to

- Determine the pharmacokinetics, tissue distribution and imaging characteristics of the antibody so as to determine the optimal biologic dose.
- Determine the efficacy of the antibody in patients with metastatic cancer.

Patient selection

Twenty six patients with metastatic colorectal cancer will be enrolled in this study. Entry criteria include adequate renal, hepatic and haematological function as well as the presence of measurable metastatic

disease. The St Vincent's Hospital human ethics committee, Sydney, Australia approved the study protocol in June 1998. The first patient was enrolled on 5th August, 1998 and to date 17 patients have received treatment. The patient's ages have ranged from 37-75 years. The sites of metastases have included the liver, lungs, and lymph nodes. Two patients have not had their primary cancer resected at the time of treatment.

Summary of Trial

The first four patients received 3mg of 123I 1110 MBq (30 mCi) labelled antibody. Subsequent patients have been enrolled in the dose escalation phase of the study in which approximately 4-5 patients receive unlabelled antibody at each dose level prior to escalation to the next dose of treatment. Following the infusion of unlabelled antibody a number of patients have also received a 3mg dose of 123I labelled antibody. Patients have been selected for treatment with 123I labelled antibody based on their age, extent of disease and performance status. The following table summarises the number of patients who have received each dose of antibody.

Dose of cold c30.6	Dose of ^{123}I c30.6	No. of patients
0	~ 3 mg	4
10.0 mg/m^2 (13.8-16mg)	~ 3 mg	3
	0 mg	2
25.0 mg/m^2 (40-48mg)	~ 3 mg	2
	0 mg	3
50 mg/m^2 (90-100mg)	~ 3 mg	3, but still in progress
100 mg/m^2	~ 3 mg	In progress

The ^{123}I-30.6 (30mCi) has been injected by slow iv push. Unlabelled c30.6 is administered as an infusion in 100-500 mls of 0.9% sodium chloride at a rate of no greater than 50 mg per hour. To date, five separate batches of antibody have been used.

Imaging

For patients receiving 123I labelled antibody whole body planar images have been obtained at 0, 4, 24 and 48 hours post injection. Single

photon emission computed tomography (SPECT) has been obtained at 24 and 48 hours post injection.

Pharmacokinetics and HACA

Serial blood samples have been collected to assess the rate of clearance of the antibody, its in-vivo stability, haematology, biochemistry and HACA. At this stage the antibody has not caused a significant change in the LFTs, haematology or biochemistry. No patients have developed HACA. The half life of the unlabelled antibody has been determined using an in house assay.

Toxicity

The patterns of side effects in the first 14 patients were variable and included skin reactions, rigors, headache, tumour pain, and nausea. The skin reactions consisted of burning erythema of the face, chest, neck, genitals, palms and soles. This reaction was often accompanied by conjunctival injection, itching of the external auditory canal, injection of nasal mucosa, stuffy nose, and discomfort or burning around the lips and throat. Typically the skin reaction occurred 30 minutes after the onset of the infusion and lasted up to 4 hours. Although the symptoms were self-limiting and did not require admission to hospital their severity in some patients was severe and required narcotic analgesics (Morphine subcutaneously) to relieve the "burning pain". Premedication with Loratidine (5-10mg) and panadol (2 tabs) did not appear to alter the severity or frequency of skin reaction. Once the erythema and pain had begun treatment with intravenous phenergan (H1 anti-histamine) or hydrocortisone provided minimal relief. The following table summarises the frequency and severity of reactions observed in the first 14 patients.

Total dose of c30.6	No. of patients	Incidence of side effects	Severity of reaction	No. receiving premedχ.
2.1-3.1 mg	4	1 (headache and rigors)	Mild	0
16.8-21 mg	5	5 (burning erythema) 1 (Nausea), 1 (tumour pain)	Mild (3), Severe (2)	2
40-51 mg	5	4 (burning erythema) 1 (Nausea), 1 (rigors)	Mild (1), Moderate (2), Severe (2)	5

χ Loratidine and panadol

The side effects observed with c30.6 are different to that generally seen with the administration of monoclonal antibodies. The table below lists some of the side effects observed with the antibodies currently in use: Rituxan, Herceptin and Panorex.

Incidence Adverse event	Herceptin (9) (patients = 352)	Rituxan (10) (patients = 315)	Panorex (11) (Patients = 83)	Panorex (12) (Patients = 490)
Cardiovascular				
Tachycardia	5		2	
Congestive heart failure	7	32	2	3%
Hypotension				
Haematological				
Anaemia	4			
Leucopaenia	3	33		
Neutropenia		21		<1%
Thrombocytopenia		25		

Adverse event	Herceptin (9) (patients = 352)	Rituxan (10) (patients = 315)	Panorex (11) (Patients = 83)	Panorex (12) (Patients = 490)
Gastrointestinal				
Nausea	33	55		10%
Diarrhoea	25		7	19%
Vomiting	23	23		5%
Nausea/Vomiting	8		4	
Anorexia	14			
Mucositis				2%
Abdominal pain	22	18	3	
Respiratory				
Increased cough	26			
Dyspnoea	22			
Rhinitis		25		
Bronchospasm		24		
Skin				
Rash		31		
Urticaria		24		
Pruritus		32		
Flushing			7	5%
Alopecia				1%
General				
Tumour pain	47		1	
Asthenia	42			8%
Fever	36	154	4	3%
Chills	32	102	4	4
Headache	26	43	2	2
Back pain	22			
Flu-like syndrome	10			
Allergic reaction	3		6	6

Skin reactions have previously been reported with the administration of antibodies. These reactions were usually mild, infrequent and qualitatively different to that observed in association with c30.6. Of particular note was the severe burning erythema of the face, chest, neck,

genitals, palms and soles following the c30.6 administration. Prior to the identification of an appropriate premedication the skin reaction was a dose limiting toxicity of c30.6 infusions. An additional point of distinction between the skin reactions observed with other antibodies and that of c30.6 is that the former can be controlled by the administration of relatively low doses of H1 anti-histamines. The burning erythema observed with c30.6 administration could not prevented or controlled with standard doses of H1 anti-histamines (Loratidine 10mg).

Some of the symptoms notably the facial flushing associated with the administration of c30.6 bore similarity to those observed following scombroid fish poisoning (11, 13). Since histamine contamination of spoiled fish is implicated in the aetiology of the latter syndrome we elected to pre-medicate patients with both H2 (Zantac 50mg iv) and large doses of H1 (phenergan 75mg im) antagonists. These drugs were administered at least 60 minutes prior to the infusion of c30.6. To date three patients have received this pre-medication and were then infused with 90-100 mg of c30.6. No side effects were observed in the first patient. The second and third patients had a mild reaction which included sneezing, facial flush and genital burning pain. We propose that infusions of c30.6 must not be administered without premedication with H1 and H2 receptor antagonists (eg Phenergan and Zantac respectively).

To our knowledge the constellation of skin reactions associated with infusion of c30.6 has not been described with the administration of monoclonal antibodies or with other drugs. The syndrome does somewhat resemble that associated with scombroid poisoning. Scombrotoxic fish poisoning is associated with the consumption of fish are contaminated with histidine. It is postulated that bacteria in the contaminated fish produce histidine decarboxylase which converts histidine to histamine. The histamine causes rash, headache, vomiting, diarrhoea and oral burning between 10 minutes and 2 hours of eating the fish (12). However, unlike with c30.6 infusions the symptoms of scombrotoxic fish poisoning responded to H1 receptor antagonist therapy.

We are currently seeking to determine the etiology of this clinical syndrome by analysis of histamine and other products of mast cell

degranulation (eg tryptase) in the serum and urine of patients administered with c30.6.

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

Dated this seventh day of June 1999

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